REMARKS

Reconsideration and withdrawal of the rejections set forth in the final Office action dated June 16, 2005 are respectfully requested in view of the arguments presented herein. A three month extension of time accompanies this response; this Amendment is thus timely filed.

I. Rejection Under 35 U.S.C. §103

The Examiner has rejected Claims 1-19, 22-26, 31-33, 35-42, and 44-45 under 35 U.S.C. §103(a). It is the Examiner's position that the above claims are obvious in view of Dolence, U.S. Patent No. 5,650,234. This rejection is respectfully traversed for the following reasons.

A. Characterization of the Invention

The present invention is directed to benzotriazolyl carbonate ("BTC") esters of water-soluble polymers such as polyethylene glycol or "PEG", prepared by a method which offers numerous advantages over known prior art methods.

The BTC esters of the invention are prepared by reacting a water-soluble polymer having at least one terminal hydroxyl group with di-(1-benzotriazolyl)carbonate ("di-BTC") to form the corresponding BTC ester of the water soluble polymer. As described on page 2 of the application (lines 21-29), the method of the present invention avoids the problems associated with the use of phosgene, to thereby provide products that do not exhibit degradation of the polymer backbone – a common occurrence in synthetic methodologies which rely on the use of phosgene for preparing polymer carbonates. Moreover, the method of the present invention is effective to form PEG-BTC ester compositions that are *free* from high molecular weight PEG-carbonate polymer side-products. This is in contrast to PEG BTC esters prepared by the method of Dolence (U.S. Patent NO. 5,650,234, referred to herein as "Dolence"), as described in Example 1of Dolence.

B. Characterization of the Art

1. Dolence (U.S. Patent No. 5,650,234) is directed to certain activated polyethylene glycols of "PEGs", more specifically, PEG carbonates, e.g., for use in a continuous coating process for covalently bound heparin on a microporous hollow fiber surface.

Dolence describes several carbonate-based polyalkylene oxides corresponding to the following structure:

$$R_5\text{-}(C\text{-}R_4)_a\text{-}(O\text{-}R_3)_b\text{-}(O\text{-}R_2)_c\text{-}O\text{-}C(O)\text{-}O\text{-}R_4,$$

where

R_1 is an N-benzotriazole group, an N-2 pyrrolidone group, or a 2-oxypyrimidine group,

R_2, R_3, and R_4 are independently selected lower alkylene groups, such as (-CH_2CH_2- or –$CH_2CH(CH_3)$-,

R5 is selected from hydrogen, methyl, a carbonyloxy-N-benzotriazole group, a carbonyloxy-N-2-pyrrolidinone group, or a carbonyl-2-oxypyrimidine group,

a is an integer between 1 and 1000,

each of b and c is an integer between 0 and 1000, such that the sum of a, b, and c is between 3 and 1000.

Dolence is additionally directed to synthesis of the subject carbonates. For preparing a PEG-benzotriazolyl carbonate ("BTC"), Dolence describes only the reaction of a PEG-diol with phosgene and hydroxylbenzotriazole to yield the corresponding PEG BTC ester. See Example 1. Moreover, the method of Dolence results in formation of a PEG-BTC product containing a high molecular weight PEG carbonate impurity, as described in Example 1, lines 54-56.

2. Catalog, Shearwater Polymers, Inc., "Polyethylene Glyol Derivatives", 2000, page 8. While the Examiner cites the Shearwater Catalog, 2000, page 8, in the outstanding Office action, in view of the remarks contained therein surrounding the disclosure of branched PEGs, it is respectfully submitted that the Examiner meant to rely upon Shearwater's 1997-1998 Catalog, (also submitted by the Applicant), since page 8 of the 1997-1997 version of the Catalog describes star and branched (multi-armed) PEGs, while the 2000 version does not. Confirmation of such assumption is respectfully requested. The following remarks are therefore based upon page 8 of the 1997-1998 Catalog.

Page 8 of the Shearwater Catalog, 1997-1998, describes commercially available star PEGs made by polymerization of ethylene oxide from a cross-linked vinyl benzene core as well as multi-armed PEGs prepared by ethoxylation of various polyols having 3 to 8 arms.

Page 8 of the Shearwater Catalog, 1997-1998, has nothing to do with BTC esters, but rather describes various branched PEG structures, where the PEG-chains are terminated by hydroxyl groups.

C. Argument.

In considering the art relied upon by the Examiner, the issue at hand is whether there is an unobvious difference between the claimed product and the prior art product. In instances in which the prior art appears on its face to describe the same or a similar product to a claimed product, the burden shifts to the Applicant to provide a comparison between the two to establish an unobvious difference. (*Ex parte Gray*, 10 USPQ2d 1922, Bd Pat. App. & Inter. 1989; *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292, Fed. Cir. 1983). In keeping with the above, accompanying this Amendment are Exhibits A-G, along with a Declaration by Dr. Samuel McManus, demonstrating the unobvious differences between the Dolence product and the product of the subject claims.

1. Unobvious Nature of Claimed Invention.

First, in addressing the unobvious nature of the products of the instant invention, nowhere does Dolence point to *any* problems associated with the described synthesis of polymer BTC esters using phosgene and hydroxybenzotriazole. Nowhere does Dolence acknowledge or even recognize the problem of HCl-promoted polymer chain cleavage due to the use of phosgene, which can lead to products having increased polydispersities. Further, nowhere does Dolence discuss in detail the problems associated with forming a PEG-BTC product containing a high molecular weight PEG-carbonate impurity.

As shown in Exhibit G, the high molecular weight PEG carbonate impurity reported by Dolence in Example 1 results from an initial reaction of PEG-di-chloroformate, A, with HO-PEG-chloroformate, B, to form a reactive intermediate species, a PEG dimer having an internal carbonate functionality and terminal chloroformate groups, C. This reactive dimer can then react with various other reactive PEG species having a terminal –OH group to form a high molecular weight PEG carbonate species having chloroformate termini, D. Upon addition of N-hydroxybenzotriazole to the reaction mixture, the chloroformate end groups are converted to benzotriazolyl termini to produce a high molecular weight PEG impurity having internal carbonate linkages, E. This series of side reactions shown in Exhibit G, associated with the Dolence method, are completely avoided when using the method of the present invention – thus leading to two very chemically distinct end-products as supported by the evidence in Exhibits A-F.

In contrast to Dolence, the present invention is directed to overcoming the shortcomings of the prior art by providing (i) a method which avoids the use of the volatile and hazardous reagent, phosgene, and (ii) high quality polymer products that are substantially absent both polymer chain degradation products and high molecular weight PEG carbonate contaminating species, such as those produced by the method described by Dolence. Thus, the Applicants not only recognized one or more problems that were previously unrecognized in the art, but additionally provided a solution thereto by virtue of the present synthetic methodology and chemically distinct products produced thereby.

2. Evidence in Support of Unobvious Differences between Claimed Product and Prior Art Product

Accompanying this Amendment is scientific evidence (Exhibits A and B) demonstrating the unobvious differences between the prior art product relied upon by the Examiner (Dolence Product) and the claimed product.

As stated previously, it is submitted that the differences between the prior art product and the claimed product are indeed unobvious, since nowhere does Dolence point to *any* problems associated with the polymer BTC esters described therein, let alone point to the specific problems associated with either the formation of polymer carbonate impurities or with polymer chain cleavage resulting from the use of the reagents employed. Moreover, the PEG BTC esters produced by the Dolence method are chemically distinct from those produced by the Applicant's method.

SUMMARY OF EXHIBITS A-G ACCOMPANYING THIS AMENDMENT:

Exhibit A describes the preparation of PEG(3,400)di-BTC (referred to by Dolence as 'poly(oxyethylene)bis-(N-hydroxybenzotriazolyl)carbonate)') following the method of the claimed invention and characterization of the resulting product. The PEG starting material employed is essentially the same as that used in Example 1 of Dolence. Exhibit A further presents a comparison of the resulting mPEG BTC product to the product described in Example 1 of Dolence.

Exhibit B is a ^{1}H NMR spectrum of the mPEG(3,400)BTC product described in Exhibit A (1-9 ppm).

Exhibit C is a ^{1}H NMR spectrum of the mPEG(3,400)BTC product described in Exhibit A (expanded region 3.1-5.0 ppm).

Exhibit D is a chromatogram corresponding to the mPEG(3,400)-BTC product described in Exhibit A.

Exhibit E is a chromatogram corresponding to the mPEG(3,400)-OH starting material described in Exhibit A.

Exhibit F describes the preparation of mPEG(20,000)-BTC following the method of the claimed invention (Example 1) and the method of Dolence (Example 2) and characterization of the respective resulting products resulting from each of the methods employed. The "(20,000)" designation indicates the molecular weight of the mPEG-OH starting material.

Exhibit G presents a series of chemical reactions corresponding to the formation of the high molecular weight PEG carbonate polymer side-product which arises in the phosgene-based method of Dolence.

The experiment summarized in Exhibit A, along with supporting evidence (Exhibits B-E), demonstrates formation of a PEG-BTC product that is clearly distinguished from the product of Dolence. Specifically, the PEG-BTC product produced in accordance with the method of the invention (as embodied in claim 1) lacks detectable quantities of high molecular PEG carbonate - as evidenced by both ^{1}H NMR and size exclusion chromatography data. Thus, the end PEG-BTC products produced by the two methods, i.e., the method of Dolence and the method of the Applicant, are clearly not the same. That is to say, they differ in their chemical compositions, since the method of Dolence results in an end-product containing high molecular weight PEG-carbonate.

Further evidence in support of the unobvious nature of the claimed invention and the differences between end-products produced by the method of Dolence versus the method of the present invention are summarized in Exhibit F. Exhibit F is describes the synthesis of mPEG(20,000) BTC in accordance with the Applicant's route and that described by Dolence. The data presented therein clearly demonstrate a significant difference between the prior art product and the claimed product, which differ not only in chemical content, but also in their polydispersities. Specifically, the recrystallized (i.e., purified) prior art product was only 90% substituted with the desired

benzotriazolylcarbonate ester functionality at the PEG-hydroxy terminus, and further contained 4.3% by weight low molecular weight PEG chain degradation products. In contrast, the claimed product was 100% substituted with the desired benzotriazolylcarbonate ester functionality at the PEG-hydroxy terminus, and further contained no detectable PEG chain degradation products.

These distinguishable differences between the prior art product and claimed product as exemplified using a 20,000 dalton PEG starting material are further affirmed by the accompanying executed declaration.

In view of the arguments and data presented herein, it is submitted that the claims currently under consideration by the Examiner are non-obvious in view of the art of record, since the product encompassed by the instant claims is chemically distinct from the product of the prior art.

3. Other Cited Art. The secondary reference relied upon by the Examiner, i.e., the Shearwater Polymers Catalog, is no way makes up for the deficiencies of the primary reference, Dolence. That is to say, nowhere does the Shearwater Polymers Catalog describe a water-soluble polymer BTC ester product having the features claimed.

For the reasons presented above, it is submitted that all pending claims are patentable and unobvious in view of the cited art. Withdrawal of the outstanding rejection of the claims under 35 U.S.C. §103 is therefore respectfully requested.

II. Conclusion.

In view of the foregoing, the Applicant submits that the claims pending in the application are patentable over the art of record. A Notice of Allowance is therefore respectfully requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 493-3400.

Respectfully submitted,

Date: December 16, 2005

By: Susan T. Evans

Susan T. Evans
Registration No. 38,443
ON BEHALF OF NEKTAR THERAPEUTICS

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

EXHIBIT A

Preparation of PEG(3,400 Da)di-BTC According to the Applicant's Method

PEG(3,400 Da)-OH (MW 3,400, 10 g, 0.00588 equivalents) was dissolved in acetonitrile (50 ml) and the resulting solution was dried by distilling off solvent under reduced pressure. The dried PEG(3,400 Da)-OH was dissolved in anhydrous acetonitrile (50 ml) and di(1-benzotriazolyl) carbonate (6.25 g of 55.8% mixture, 0.001177 moles, 2 fold molar excess) and pyridine (1.9 ml) were added and the reaction mixture was stirred at room temperature under nitrogen overnight.

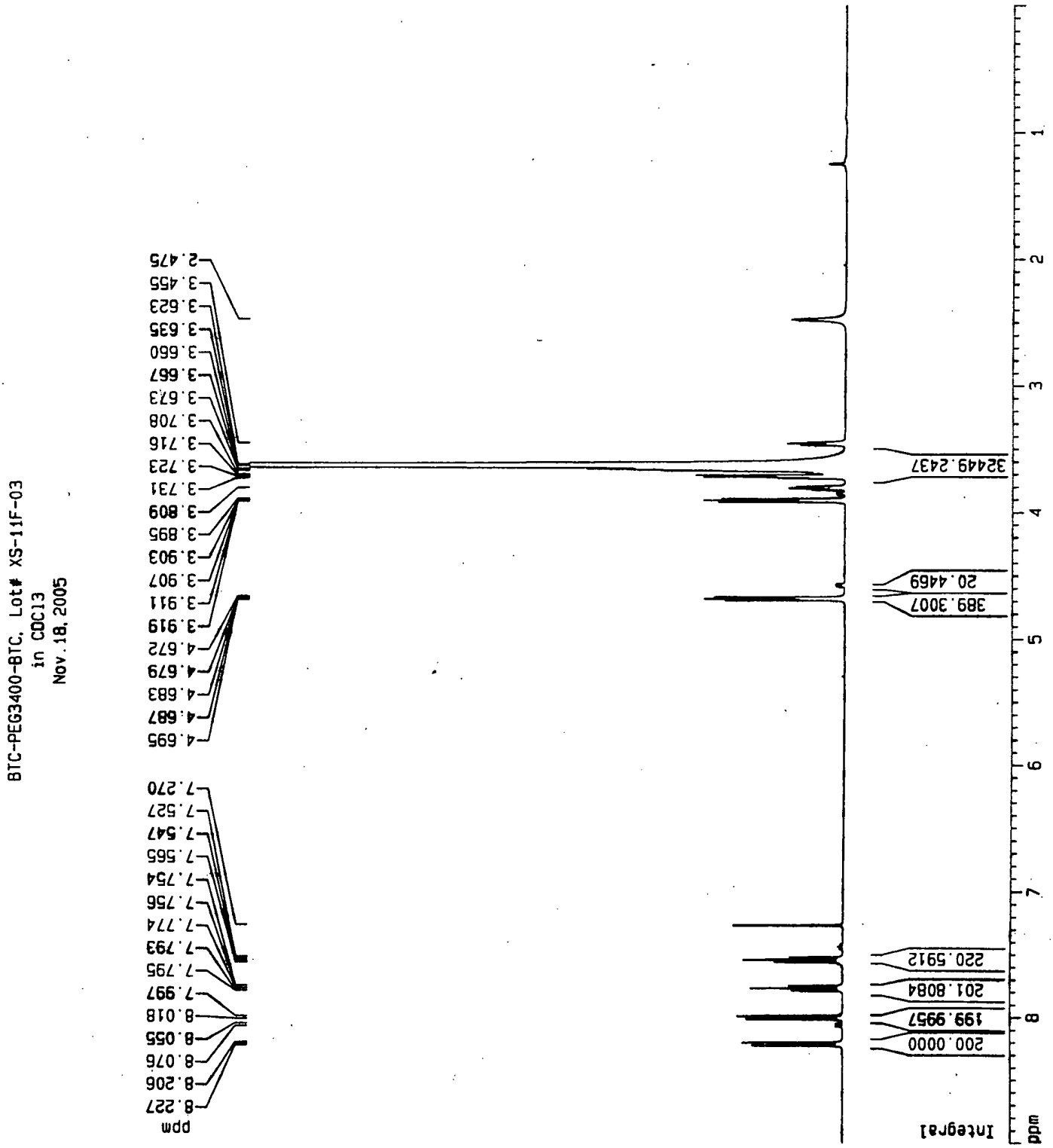
Next the solution was filtered and the solvent was distilled off under reduced pressure. The crude product was dissolved in dichloromethane (10 ml) and precipitated with ethyl ether (150 ml). The precipitated product was dried under vacuum overnight. Tthe product was dissolved in dichloromethane (5 ml) and precipitated again with isopropanol (150 ml) at 0 – 5 °C to provide 9.4 g of white solid after drying. The ^{1}H NMR analysis showed that the recovered PEG(3,400 Da)-di-BTC was 100% substituted (i.e., 100% desired product).

^{1}H NMR (d_6-DMSO): 3.51 ppm (s, polymer backbone), 4.62 ppm (m, mPEG-O-CH_2 - $\underline{CH_2}$ -OCO_2-, 4H), 7.41-8.21 ppm (complex mult, benzotriazole protons, 8H). No peak was observed at ~ 4.28 ppm (corresponding to high molecular weight PEG carbonate polymer). See Exhibit C.

^{1}H NMR performed in $CDCl_3$ as a solvent (Exhibit B) correspond to those reported in Example 1 of US 5,650,234 (3.46 ppm (m, ^{13}C isotope side band), 3.65 ppm (s, PEG backbone), 3.81 (m, ^{13}C isotope side band), 3.91 ppm (m, mPEG-O-CH_2 - $\underline{CH_2}$ -OCO_2-), 4.57 (m, mPEG-O-CH_2 - $\underline{CH_2}$ -OCO_2--possible conformational isomer), 4.68 ppm (m, mPEG-O-CH_2 - $\underline{CH_2}$ -OCO_2-), 7.55 ppm (m, aromatic H,), 7. 77 ppm (m, aromatic H), 8.00 ppm (m, aromatic H), 8.22 ppm (m, aromatic H)), with the exception of the absence of a peak at 4.28 ppm.

Size exclusion chromatography confirmed that the product (Exhibit D) possessed the same molecular weight distribution as the starting PEG(3,400 Da)-OH (Exhibit E). No high molecular weight material was detected.

EXHIBIT B


BTC-PEG3400-BTC, Lot# XS-11F-03
in CDCl3
Nov.18, 2005
ppm
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8.206
8.076
8.055
8.018
7.997
7.795
7.793
7.774
7.756
7.754
7.565
7.547
7.527
7.270
4.695
4.687
4.683
4.679
4.672
3.919
3.911
3.907
3.903
3.895
3.809
3.731
3.723
3.716
3.708
3.673
3.667
3.660
3.635
3.623
3.455
2.475
Integral
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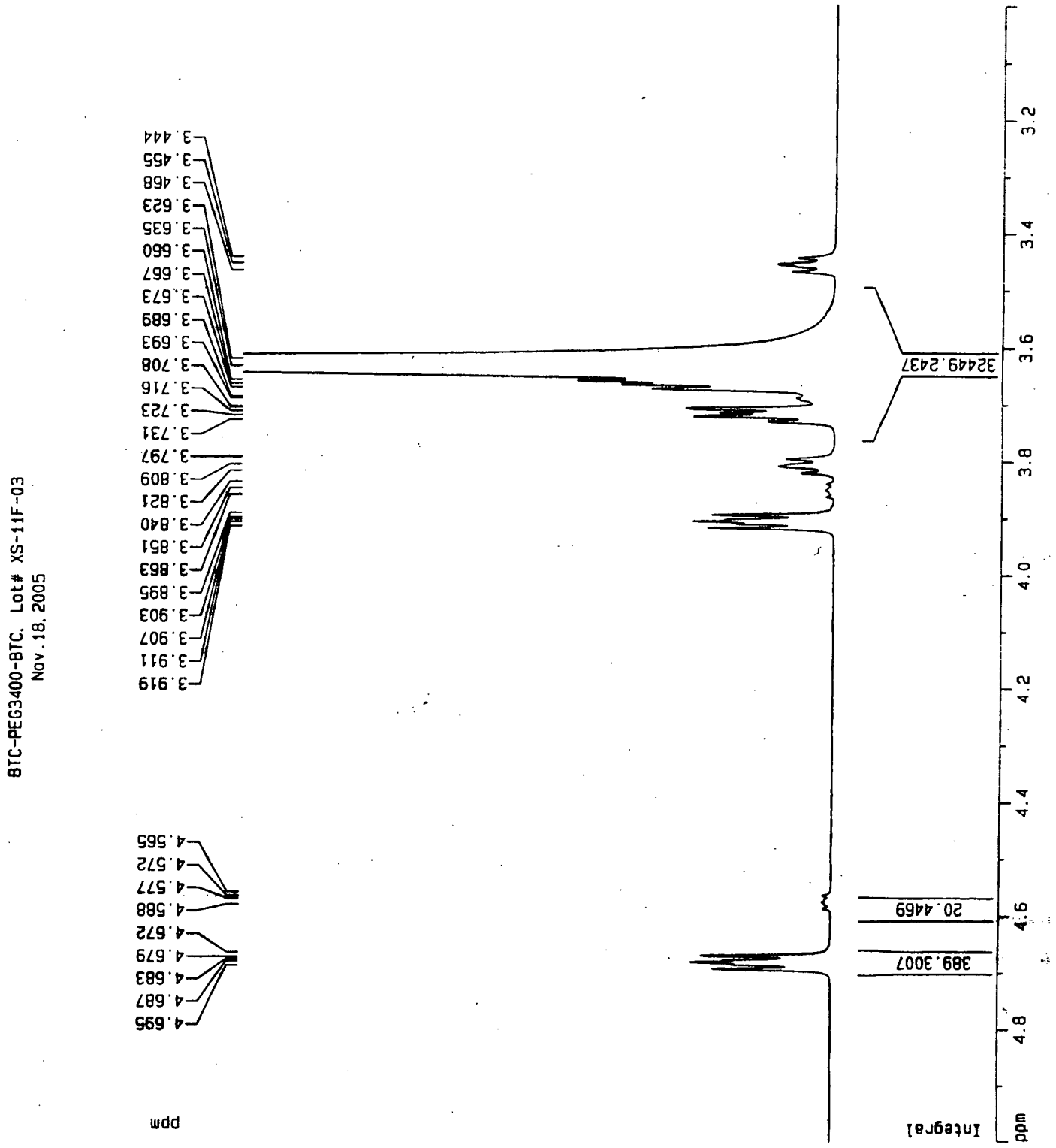
199.9957
200.0000
ppm

EXHIBIT C


BTC-PEG3400-BTC, Lot# XS-11F-03
Nov.18, 2005
ppm
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3.455
3.468
3.623
3.635
3.660
3.667
3.673
3.689
3.693
3.708
3.716
3.723
3.731
3.797
3.809
3.821
3.840
3.851
3.863
3.895
3.903
3.907
3.911
3.919
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32449.2437
20.4469
389.3007
ppm
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8

Current Date 11/14/05 Project QC_LC_003_2005_Q3 Sample Set Name 111105

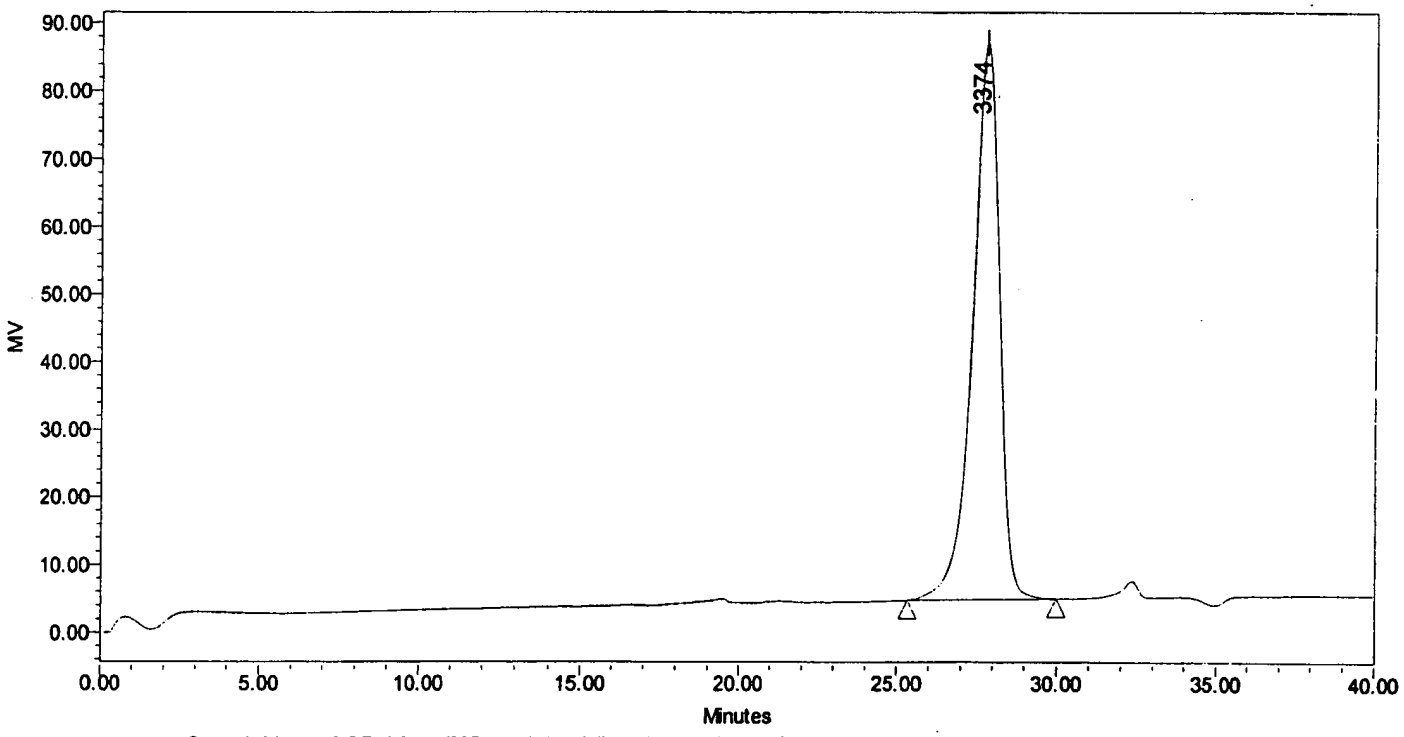
Sample Information

EXHIBIT D

SampleComments BTC-3400-BTC

SampleName	AR&D 3354 (XS-11F-03)	Sample Type	Broad Unknown
Vial	29	Date Acquired	11/11/05 5:25:20 PM
Injection	1	Acq Method Set	MIXD2GPC LOW
Injection Volume	30.00 ul	Processing Method	MIXD CAL LOW
Channel	410	Date Processed	11/14/05 8:13:58 AM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram



SampleName ARD 3354 (XS-11F-03) Vial 29 Injection 1 Channel 410 Date Acquired 11/11/05 5:25:20 PM

GPC Results

	Dist Name	Area	% Area	Retention Time	Mn	Mw	MP	Mz	Mz+1	Poly dispersity
1		4787628	100.00	27.771	3417	3525	3374	3649	3797	1.031546

050LC -003

Analyst _____ *Notebook* _____

Date _____ *Page* _____

Current Date 11/7/05 Project QC_LC_003_2005_Q3 Sample Set Name 110705

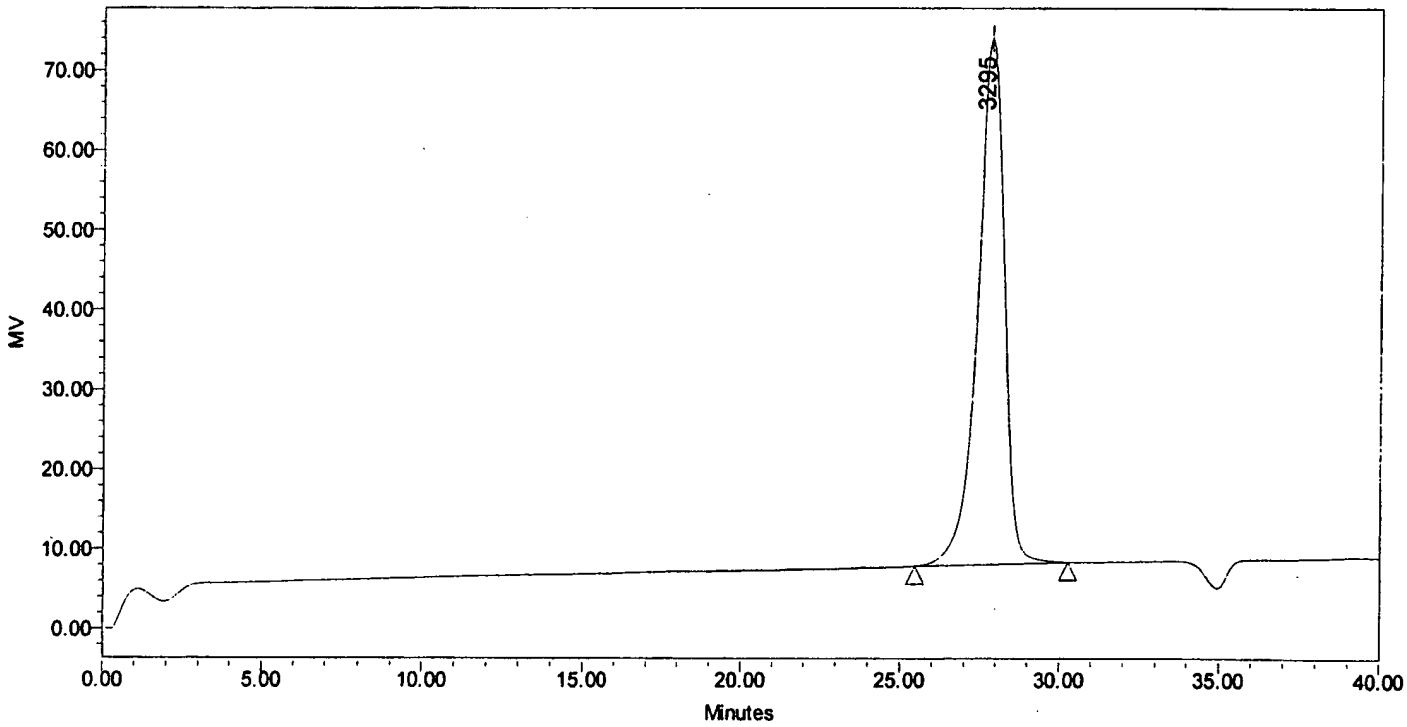
Sample Information

EXHIBIT E

SampleComments 733275

SampleName	PEG 3400	Sample Type	Broad Unknown
Vial	35	Date Acquired	11/7/05 12:53:29 PM
Injection	1	Acq Method Set	MIXD2GPC HIGH
Injection Volume	30.00 ul	Processing Method	MIXD CAL LOW
Channel	410	Date Processed	11/7/05 1:57:08 PM
Run Time	40.0 Minutes		

Auto-Scaled Chromatogram



SampleName PEG 3400 Vial 35 Injection 1 Channel 410 Date Acquired 11/7/05 12:53:29 PM

GPC Results

	Dist Name	Area	% Area	Retention Time	Mn	Mw	MP	Mz	Mz+1	Poly dispersity
1		3850590	100.00	27.832	3326	3433	3295	3551	3688	1.031983

050LC -003

Analyst _____ *Notebook* _____

Date _____ *Page* _____

EXHIBIT F

PREPARATION OF MPEG(20,000 DA)-BTC - ROUTE 1 (APPLICANT'S ROUTE).

The polymer reagent, mPEG(20,000 Da-BTC, where BTC equals benzotriazolylcarbonate, was prepared in accordance with the method described in the U.S. Patent Application No. 10/727,337.

mPEG(20,000 Da)-OH (MW 20,000, 5 g, 0.00025 moles) was dissolved in toluene (80 ml), and the resulting solution was then dried by removing the solvent by distillation under reduced pressure. The dried mPEG(20,000 Da)-OH was subsequently dissolved in anhydrous acetonitrile (70 ml), to which was added di(1-benzotriazolyl) carbonate (0.22 g of 70% mixture, 0.00052 moles), and pyridine (3.0 ml), and the reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight.

The solution was concentrated under reduced pressure, and the crude product precipitated by addition of isopropanol. The recovered product was then dissolved in dichloromethane, followed by precipitation by addition of isopropanol to provide 4.4 g of white solid after drying.

PRODUCT CHARACTERIZATION. ^{1}H NMR analysis revealed that the recovered mPEG(20,000) BTC product was 100% substituted (i.e., 100% desired product). ^{1}H NMR (d_6-DMSO): 3.23 ppm (s, -OCH_3, 3H), 3.51 ppm (s, polymer backbone), 4.62 ppm (m, mPEG-O-CH_2 -OCO_2-, 2H), 7.41-8.21 ppm (complex mult, benzotriazole protons, 4H).

Size exclusion chromatography confirmed that the product had the same molecular weight distribution as the starting material, mPEG(20,000 Da)-OH, indicating that no significant polymer chain cleavage occurred during the synthesis. No low molecular weight polymer material was detected.

PREPARATION OF MPEG(20,000 DA)-BTC - ROUTE 2 (DOLENCE ROUTE)

The polymer reagent, mPEG(20,000 Da-BTC, where BTC equals benzotriazolylcarbonate, was prepared using the method described in the U.S. Patent No. 5,650,234 (Dolence).

mPEG(20,000 Da)-OH (MW 20,000, 5 g, 0.00025 moles) was dissolved in toluene (80 ml), and the resulting solution was dried by removing solvent by distillation under reduced pressure. The drying process was then repeated. Dried mPEG(20,000 Da)-OH was then dissolved in a mixture of anhydrous toluene (70 ml) and dichloromethane (10 ml), to which was added 0.64 ml (0.00121 moles) of a 20% solution of phosgene in toluene, and the resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere. The solvents and excess of phosgene were removed by distillation under reduced pressure. The remaining solid residue was dissolved in anhydrous acetonitrile (50 ml), to which was added 1-hydroxybenzotriazole (0.19 g, 0.00141 moles), following by addition of triethylamine (0.086 ml). The resulting mixture was then stirred overnight at room temperature under a nitrogen atmosphere. The solution was concentrated, and the product precipitated by addition of isopropanol (250 ml). The precipitated product was recovered by filtration and dried under vacuum to provide 4.3 g of a white solid material.

PRODUCT CHARACTERIZATION. ^{1}H NMR analysis revealed that the product, mPEG(20,000) BTC, was 90% substituted (i.e., 90% of desired product or 90% pure). ^{1}H NMR (d_6-DMSO): 3.23 ppm (s, -OCH_3, 3H), 3.51 ppm (s, polymer backbone), 4.62 ppm (m, mPEG-O-CH_2 -OCO_2-, 2H), 7.41-8.21 ppm (complex mult, benzotriazole protons, 4H).

Size exclusion chromatography confirmed the presence of 4.3% of low molecular weight PEG-derived material, thus indicating that detectable amounts of PEG-chain cleavage occurred during the synthesis.

EXHIBIT G

Series of reactions corresponding to formation of a high molecular weight PEG carbonate side-product which arises when using the phosgene-based method of Dolence.